REMARKS

Claims 7, 18-20, and 34-47 are pending. Claims 7, 34, 40, and 44 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting. Claims 7, 18-20, and 34-47 are rejected under 35 U.S.C. § 112, first paragraph. Applicants address each of these rejections as follows.

Amendments to the Claims

Claims 7, 34, 40, and 44 have been amended to recite that the second polypeptide includes a granulocyte colony stimulating factor receptor, or a granulocyte colony stimulating factor receptor deficient in amino acid residues 5 (Glu) through 195 (Leu) of wild-type granulocyte colony stimulating factor receptor, or a granulocyte colony stimulating factor receptor deficient in amino acid residues 5 (Glu) through 195 (Leu) and amino acid residues 725 through 756 of wild-type granulocyte colony stimulating factor receptor. Support for this amendment is found, for example, at page 9, lines 16-24, of the specification. Claims 7, 34, 40, and 44 have also been amended to recite a "granulocyte colony stimulating factor" receptor. Support for this amendment is found, for example, at page 4, lines 19-22, and page 6, lines 9-12, of the specification. Claims 7, 34, 40, and 44, as amended, recite "blood cells." This amendment finds support, for example, at page 7, lines 13-20, of the specification. The particular steroid hormone receptors added to claims 18, 35, 41, and 45 find support, for example, at page 6, lines 4-7, of the

specification. No new matter has been added by the present amendments.

Claims 19, 20, 36, 39, 42, 43, 46, and 47 have been canceled. Applicants reserve the right to pursue canceled subject matter in this or a continuing application.

Objection to the Title

The Office asserts that the Title is not descriptive of the claimed invention. Applicants submit that the present amendment to the Title overcomes this basis for objection.

New Matter

The Office objects to the amendment filed March 2, 2005, particularly the changes made to page 2 of the disclosure, as introducing new matter into the specification. According to the Office, the added material is not supported by the original disclosure. The present application is the U.S. National Stage of PCT/JP97/00687, filed March 5, 1997 and, therefore, the specification of the present application is identical to that of PCT/JP97/00687.

Applicants, herewith, submit a Declaration by Ms. Mikiko Oyanagi who is familiar with both the English and the Japanese languages. In this Declaration (paragraphs 3-5) Ms. Oyanagi states that the paragraph at page 2, lines 12-15, of PCT/JP97/00687 is correctly translated as (emphasis added):

> The present invention seeks to overcome the problem of poor gene introduction efficiency by selectively amplifying *in vivo* or *ex vivo* hematopoietic stem cells into which a gene for treatment has been introduced. An objective of the invention is to provide a fundamental technique for gene therapy targeting hematopoietic stem cells, and such.

And that the above paragraph, in the translation of PCT/JP97/00687 filed at the time of U.S. national stage entry, was incorrectly translated as follows (emphasis added):

> The present invention seeks to overcome the problem of poor gene introduction efficiency by selectively amplifying *in vivo* or *ex vivo* hematopoietic stem cells into which a gene for treatment has been introduced. The objective of the invention is to provide a fundamental technique for gene therapy targeting hematopoietic stem cells.

Accordingly, the Oyanagi Declaration supports Applicants' contention that the amendment "An objective of the invention is to provide a fundamental technique for gene therapy targeting hematopoietic stem cells, and such" does not introduce new matter and merely corrects a translational error occurred at the time of preparing the English specification from the original Japanese specification. This basis for rejection should be withdrawn.

Provisional Obviousness-Type Double Patenting

Claims 7, 34, 40, and 44 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 9 of co-pending Application No. 09/577,084. Applicants submit that, in view of the present

amendment to claims 7, 34, 40, and 44, this basis for rejection may be withdrawn.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 7, 18-20, and 34-47 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description and enablement requirements. Claims 19, 20, 36, 39, 42, 43, 46, and 47 have been canceled; the rejection of these claims is moot. Applicants address the rejections as they relate to the pending claims as follows.

Written Description

Claims 7, 18-20, and 34-47 are rejected under 35 U.S.C. § 112, first paragraph, for an asserted lack of written description in the specification as filed. The Office lists the headings for Examples 1-6 of the specification and states (page 7):

> As can be seen above, none of the examples are directed to the selective proliferation of a cell, e.g., gene therapy, in a mixed/heterogeneous assay. A review of the disclosure fails to find an adequate written description of the reagents used to practice the claimed method.

Applicants disagree.

As an initial matter, Applicants note that the claims, as amended, are directed to methods of causing selective proliferation of a blood cell. In addition, the claims require that the second polypeptide includes a granulocyte colony stimulating factor ("G-CSF") receptor, or a granulocyte colony stimulating factor receptor deficient in amino acid residues 5 (Glu) through 195 (Leu) of wild-type granulocyte colony stimulating factor

receptor, or a granulocyte colony stimulating factor receptor deficient in amino acid residues 5 (Glu) through 195 (Leu) and amino acid residues 725 through 756 of wild-type granulocyte colony stimulating factor receptor.

An objective standard for determining compliance with the written description requirement, as stated by the Federal Circuit, is "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 U.S.P.Q.2d 1614, 1618 (Fed. Cir. 1989) (see also M.P.E.P. § 2613.02). To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he was in possession of the invention now claimed. In addition, as set forth in M.P.E.P. § 2163.04, a description is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the Examiner to rebut the presumption. In this case, the Office has clearly failed to meet this standard.

As discussed in Applicants' previous response, the specification is replete with implicit and explicit references to a method for causing the selective proliferation of a blood cell, both in the context of *in vitro* manipulation and *in vivo* gene therapy. This concept is unambiguously set forth in the first lines of the specification: "The present invention relates to the field of genetic engineering, ***particularly the field of gene therapy***" (page 1, lines 4-5, emphasis added). Additional description for the method for causing selective proliferation of a blood cell, as presently claimed, *in vivo* or *in vitro* is

found in the specification as originally filed, particularly at:

- Page 2, lines 2-4 ("It has thus been desired to establish a system that *enables selective amplification of cells containing an introduced gene*.");

- Page 2, lines 23-26 ("The present invention seeks to overcome the problem of poor gene introduction efficiency by selectively amplifying *in vivo* or *ex vivo* hematopoietic stem cells into which a gene for treatment has been introduced.");

- Page 3, lines 2-11 ("In the *field of gene therapy* today, there are numerous problems to be overcome concerning the efficiency of gene introduction into target cells and the expression efficiency of the introduced gene. It is therefore obvious that *establishing a system for selectively amplifying only the target cells containing the introduced gene* will produce a major breakthrough . . . [and] would contribute significantly to the *field of gene therapy*.");

- Page 3, line 15 - page 4, line 2 ("Considering these facts, the present inventors have thought of a *system for amplifying hematopoietic stem cells* through dimerization of a genetically engineered *G-CSF receptor* . . . Thus, the present invention was completed by developing a new system for *selectively amplifying hematopoietic stem cells* into which a gene has been introduced by *activating the G-CSF receptor portion of the chimeric gene* product through external stimulation with estrogen.");

- Page 7, lines 13-15 ("[I]n the present invention, the cell into which the vector is introduced includes hematopoietic stem cells, lymphocyte, and cells other than these blood cells."); and

- Page 15, lines 5-12 ("The present invention has made it possible to selectively amplify a cell into which an exogenous gene has been introduced, in response to an external stimulus, *thereby enabling effective gene therapy even when the introduction efficiency of the gene into the target cells is low*. Furthermore, since the system for selectively amplifying cells of the present invention can be applied to various blood cells, the range of cells targeted in gene therapy has been widened.").

In light of the above, Applicants submit that one skilled in the art, looking at the

specification as filed, would be apprised of the scope of the present invention, and more particularly of Applicants' possession of a method for causing selective proliferation of a blood cell, *in vivo* or *in vitro*, utilizing a chimeric gene or protein containing G-CSF receptor sequence and/or vector as claimed. In fact, it is readily apparent that the instant specification reasonably conveys to a person of ordinary skill in the art that Applicants were in possession of the claimed invention, in accordance with the encompassed scope and limitations in question.

Moreover, Applicants submit that the Office's assertion that "none of the examples are directed to the selective proliferation of a cell, e.g., gene therapy, in a mixed/heterogeneous assay" is erroneous. For instance, in Example 6, Applicants describe collecting bone marrow from mouse femurs, isolating mononuclear cells, introducing constructs encompassed the present claims into the cells and selectively proliferating the cells. Applicants state that "[a]mong the bone marrow cells infected with "vMXGCRER" or "vMXGCRΔ(5-195)/ER," granulocyte-macrophage lineage colonies and erythroblast lineage colonies, which had differentiated from the bone marrow cells by the estradiol stimulation, were observed" (see page 14, lines 15-18, of the specification). Clearly Applicants describe selectively proliferating blood cells obtained from a heterogeneous population as well as the reagents required for this method.

Finally, Applicants note that the Office states (page 7):

Also not apparent is a written description of the best mode contemplated by

applicant for practicing the invention.

On this point, Applicants first note that at page 9, line 9, the specification states "Best Mode for Implementing the Invention" and that this statement is followed by Examples 1-6. Given, as noted above, that Applicants, for instance in Example 6, describe how one skilled in the art can practice the claimed invention, and that Applicants present this as the best mode for implementing the invention, this basis for rejection should be withdrawn.

In sum, Applicants submit that the Office has failed to demonstrate that one skilled in the art, upon reading the specification, would not recognize that Applicants have invented what is claimed. The written description rejection should be withdrawn.

Enablement

Claims 7, 18-20, and 34-47 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which is not described in the specification in such a way as to enable one skilled in the art to make and use the invention. In particular, the Office states (page 9):

> The claimed invention clearly relates to the area of gene therapy. While much research has been and is continuing in this area [sic], the art is recognized [a]s being rife with serious issues of enablement.

In support of this assertion, the Office cites a January 13, 2003 letter from NIH director Patterson and states (page 9):

> It is noted that in the nearly seven years since the filing date of the instant application, the ability to effectively treat blood cells, much less a broader genus of cells, in just one life form, has been met with much difficulty, and that the NIH was recommending that ... such investigations be "discontinued."

Applicants submit that the claims, as amended, are free of this basis for rejection.

The test of enablement is whether one reasonably skilled in the art could make or use the claimed invention from the disclosures in the specification, coupled with information known in the art, without *undue experimentation*. See M.P.E.P. § 2164.01 and *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 U.S.P.Q.2d 1217, 1233 (Fed. Cir. 1988). A specification is *presumed* to be in compliance with the enablement requirement of 112, first paragraph; the burden is on the Patent Office to establish a reasonable basis to question enablement. For an Examiner to sustain a rejection on the grounds of enablement, the Examiner must provide *evidence* that the claimed method could not be performed without undue experimentation (see M.P.E.P. § 2164.01(a)).

In the present case, the Office's argument for lack of enablement centers on the premise that gene therapy is risky and, therefore, unpredictable. However, the only support for this position lies in a letter from NIH Director Patterson recommending the discontinuance of investigations involving retroviral-mediated gene transfer to hematopoietic cells. It is Applicants' position that this "evidence" is not relevant, as the letter from Director Patterson goes to the *advisability* and not the *enablement* of gene therapy methods. The mere fact that a particular method might not be clinically advisable

is irrelevant to the issue of patentable enablement. Specifically, the proper standard for compliance with the enablement requirement is not *absolute predictability* (the presumed standard for determining whether a particular therapy is safe for human testing) but *objective enablement*: namely would one reasonably skilled in the art be able to make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation.

In the present case, the Office provides no evidence that the positive results obtained using murine bone marrow cells (blood cell precursors) described in Example 6 of the specification would not enable one skilled in the art to achieve similar results using bone marrow cells from other animals, such as humans, without undue experimentation. Accordingly, given the explicit disclosure of a working example of a method within the scope of the present claims, Applicants respectfully submit that one reasonably skilled in the art would be able to make and use the claimed invention without undue experimentation.

Applicants also direct the Office's attention to the enclosed Declaration by inventor Dr. Yasuji Ueda who is also an author of Hara et al. (Gene Therapy 11:1370-1377, 2004; "the Hara et al. publication;" copy enclosed with the Declaration as Exhibit 1). The Ueda Declaration states (paragraphs 3-5):

> The Hara et al. publication describes *in vivo* selective proliferation of bone marrow cells transduced with a construct (MGK/h91GE) encoding a chimeric protein having a granulocyte colony stimulating factor receptor extracellular domain with amino acids 5-195 deleted and a phenylalanine substitution for tyrosine 703 and an intracellular domain including an

> estrogen receptor hormone binding domain. The MGK/h91GE construct also contains $gp91^{phox}$ (a desired exogenous gene encoding the NADPH oxidase $gp91^{phox}$ subunit).
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> * * *
>
> Estrogen was administered to a cohort of the transplants and neutrophil superoxidase production was monitored. A significant increase in oxidase-positive cells was observed in the estrogen-treated mice, and repeated estrogen administration maintained the elevation of transduced cells for twenty weeks. Moreover, oxidase-positive neutrophils were increased in the transplants given the first estrogen at nine months post-transplantation.
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> * * *
>
> The results presented in the Hara et al. publication indicate that transduced long-term repopulating cells expressing a fusion protein containing a granulocyte colony stimulating factor receptor extracellular portion and an estrogen receptor hormone binding domain intracellular portion were maintained *in vivo* and selectively proliferated in response to estrogen stimulation.

The Ueda Declaration supports Applicants' contention that one skilled in the art could make and use a chimeric protein containing a granulocyte colony stimulating factor receptor portion and a ligand binding domain of a steroid hormone receptor to selectively proliferate blood cells *in vivo*.

For the reasons given above, Applicants submit that the scope of the presently claimed invention is commensurate with the instant specification's scope of enablement. The enablement rejection should be withdrawn.

CONCLUSION

Applicants submit that the application is now in condition for allowance and this action is hereby respectfully requested.

Enclosed is a Petition to extend the period for replying to the Office Action for three months, to and including March 16, 2006, and a check in payment of the required extension fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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